REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 28-46 are currently under consideration. Claims 28-42 and 44-46 are amended without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

The Examiner is thanked for indicating that the finality of the present application has been withdrawn and for acknowledging reception of the Sequence Listing, the Computer Readable Form of the Sequence Listing, and the Information Disclosure Statement.

The Examiner is respectfully requested to consider and make of record the article by Butel et al. titled "Clostridial pathogenicity in experimental necrotising enterocolitis in gnotobiotic quails and protective role of Bifidobacteria" and published in J Med Microbiol 47: 391-399, 1998; the article by Meer et al. titled "Human disease associated with Clostrodium perfringens enterotoxin" and published in Rev Environ Contam Toxicol 150: 75-94, 1997; the article by Klinger et al. titled "Clostridium difficile infection: risk factors, medical and surgical management" and published in Dig Dis 18: 147-160, 2000; and the article by Elmer et al. titled "Biotherapeutic agents. A neglected modality for the treatment and prevention of selected intestinal and vaginal infections" and published in JAMA 275: 870-876, 1996. These references are cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449.

It is submitted that the claims herewith are patentably distinct over the prior art, and these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims presented herein are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply to clarify the scope of protection to which Applicants are entitled.

II. OATH/DECLARATION WAS FILED ON DECEMBER 21, 2005

The Office Action alleges that a document was received on March 28, 2006 identified as an Oath and that only one page was visible. This event led to uncertainty regarding the purpose of the document. Applicants have reviewed said document through the Image File Wrapper in Patent Application Information Retrieval (PAIR), and Applicants respectfully note that the Patent and Trademark Office has stamped the reception date of said document as December 21, 2005. On December 21, 2005, Applicant indeed filed a Declaration under 37 C.F.R. § 1.132 in conjunction with an Amendment and Response to Office Action. Therefore, Applicants believe that the first page from the Declaration of December 21, 2005 was mistakenly regarded as newly filed on March 28, 2006.

III. THE PRIORITY DATE IS SEPTEMBER 12, 2000

The Office Action alleges that since no English translation of Japanese Patent Application No. 2001-287688 filed September 12, 2000 was provided, priority is thereby given the date of the parent U.S. Application No. 09/816,391 filed on March 26, 2001. Submitted herewith is a certified English translation of Japanese Patent Application No. 2001-287688 filed September 12, 2000. Accordingly, Applicants are entitled to the priority date of September 12, 2000.

Reconsideration of the priority date is respectfully requested.

IV. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH IS OVERCOME

Claims 28-46 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The rejection is respectfully traversed.

The Office Action alleges that the metes and bounds of claim 28, which is directed to a nonpathogenic gene therapy vector of an anaerobic bacterium, are unclear. In response, claim 28 is clarified to recite "a transformed nonpathogenic gene delivery vector of an anaerobic bacterium of the genus Bifidobacterium" which more distinctly discloses the invention presented in the claims.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 second paragraph is respectfully requested.

V. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH ARE OVERCOME

A. Written Description

Claims 28 and 30-34 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Office Action contends that claims 28 and 30-34 are broadly drawn and apply to a genus of Bifidobacterium Longum promoters and terminators, but the working examples only demonstrate an individual species of Bifidobacterium Longum. The Office Action asserts that the disclosure is "not sufficient to show that the Applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed."

In response, Applicants note that claim 28 has been amended as follows:

> 28. A transformed nonpathogenic bacterium of the genus Bifidobacterium which grows under anaerobic conditions and is transformed with a cloning vector, wherein said cloning vector:
>
> (1) has DNA encoding a protein (a) with anti-tumor activity, or a protein (b) that converts a precursor of an antitumor substance (P) into an antitumor substance, and a promoter and terminator functioning in a bacterium of the genus Bifidobacterium;
>
> (2) can replicate in a bacterium belonging to the genus Bifidobacterium,
>
> (3) can transform a bacterium belonging to the genus Bifidobacterium, and
>
> (4) has a selective marker that can detect specifically a bacterium belonging to the genus Bifidobacterium transformed with the cloning vector.

Support for growing the bacterium under anaerobic conditions can be found, for example, in paragraph 0016. Support for the cloning vector and its replication and transformation capabilities can be found, for example, in paragraph 0115. Support for the promoter and terminator in the cloning vector can be found in paragraph 0028. Finally, support for the

selective marker can be found, for example, in paragraph 0113. Applicants argue that one skilled in the art would recognize that the inventors were in possession of the instant invention at the time the application was filed

Notably, Brown et al. (U.S. Patent No. 6,416,754B1; hereinafter "Brown 1"), to which the Office Action refers as being related with the present invention, presents a claim relating to "nonpathogenic anaerobic microorganism" (claim 1), which is substantially broader than a bacterium of the genus Clostridium. This claim has been granted despite that the Brown 1 specification contains examples involving only one kind of bacteria (Clostridium acetobutylicum) and a cloning vector (E. coli- Clostridium cloning vector). Brown 1 is associated with the same technical category as the present invention, and further the method mentioned in Brown 1 was developed at approximately the same time as the present invention. The present invention discloses examples using one kind of bacteria (Bifidobacterium longum) and a cloning vector (E.coli - Bifidobacterium shuttle vector), which is similar to Brown 1, although the claims of the present invention are focused to a bacterium of the genus Bifidobacterium. Therefore, in view of Brown 1, one skilled in the art would recognize that the present claims are certainly supported by the written description, especially if the state of the art indicates that a description of one bacterium species is supportive of - at least- the genus, if not broader. Thus, the present claims do not contain "a subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention."

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 first paragraph is respectfully requested.

B. Enablement

Claims 28-35 and 37-41 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

According to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988),

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue

> experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted]. *Id.* at 1404.

Determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), for example: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Thus, it is respectfully submitted that for a proper Section 112, first paragraph, lack of enablement analysis, an Office Action must show that the *Wands* factors are not met. Simply, it is respectfully asserted that the lack of enablement rejection fails to provide a fact based analysis using the *Wands* factors that supports the proposition the claimed invention require **undue** experimentation.

The Examiner is respectfully reminded that a specification need not contain any example of the invention, as the issue is whether the disclosure enables one skilled in the art to practice the invention without undue experimentation. *In re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). Simply, a determination that undue experimentation is necessary to practice the invention does not necessarily follow from a lack of examples in the specification. And, the Examiner is further respectfully reminded that an applicant need not describe all actual embodiments of a claimed invention.

The Office Action alleges that while the specification does provide enablement for a method of delivering a genetically modified bacterium to a tumor wherein the bacterium is a Bifidobacterium longum, it does not provide enablement for a method of delivering a genetically modified bacterium to a tumor wherein the bacterium is selected from the group of a genus of Bifidobacterium. According to the Office Action, the specification does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope

with these claims, and cites the Wands factors in its allegation that the present application is not enabling.

More specifically, the Office Action refers to Yazawa et al. (Breast Cancer Res Treat 66:156-170, 2001; hereinafter "Yazawa 1") and Argnani et al. (Microbiology 142: 109-114, 1996; hereinafter "Argnani") and contends that these references indicate that little is known about the genetic properties of Bifidobacterium and that the genus is highly unpredictable. In response, Applicants argue that Argnani indicates that transforming Bifidobacterium is not unpredictable and, in fact, demonstrates transformation in other Bifidobacterium species. Argnani states that "application of the pretreatment and electroporation procedure described above for B animalis... to other Bifidobacterium species and strain yielded many transformant" (Argnani, page 111, right column, lines 22-26), which clearly indicates that transformation of B animalis and other Bifidobacterium strains is possible. Table 3 indicates Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, and Bifidobacterium longum as strains other than B animalis that can be used for introducing recombinant DNA. Thus, the same protocol provided by Argnani is applicable across many different Bifidobacterium strains, thereby supporting Applicants' argument that the specification of the present invention enables application to different Bifidobacterium strains.

Argnani also refers to using pDG7, an Escherichia coli-Bifidobacterium shuttle vector (page 110, left column, lines 6-9). In the present invention plasmid pBLES 100, indicated as a representative example, is also an Escherichia coli-Bifidobacterium shuttle vector. Given that Argnani alluded to introducing DNA into various strains of Bifidobacterium using an Escherichia coli-Bifidobacterium shuttle vector, a person skilled in the art would conclude that the plasmid pBLES100 could also be introduced into different microorganisms of the Bifidobacterium genus.

Yazawa 1 summarizes the results of the experiment as demonstrating that "the genus of Bifidobacterium...which is beneficial rather than nonpathogenic for its host, can be engineered" (page 169, right column, lines 19-22). Argnani states, "In this paper we describe the development of a system for efficient and reproducible genetic transformation of strains of the genus Bifidobacterium" (page 109, column right, lines 21-24). Based on these recitations, the authors, who are regarded as persons skilled in the art, perceive their work as applicable to the Bifidobacterium genus. Further, the authors' comments clearly indicate that, in the present

application, they would expect the claimed genus of Bifidobacterium could be used without undue experimentation. Hence, the Office Action does not provide evidence that the instant invention would require undue experimentation due to the prior art and unpredictability in the art.

The Office Action states that "Argnani teaches 'although electroporation technique has proven to be widely applicable to genetically transform bacterial strain, all Bifidobacterium **so far** examined have proved refractory to efficient and reproducible transformation' (page 109)" (emphasis added). The Office Action uses this statement as an indication of the unpredictability of the art. Applicants respectfully disagree, noting that this statement was based on the former state of the art **prior** to study performed by Argnani and prior to the filing of the present application. Argnani mentions that, in the study, a system was developed "for **efficient** and **reproducible** genetic transformation of strains of the genus Bifidobacterium" (page 109, column right, lines 21-24; emphasis added), which indicates that the state of the art is different following his study, i.e., at the time the present application was filed. Therefore, even if the Office Action chooses to conclude that transformation of Bifidobacterium may have been unpredictable at one time, the state of the art had clearly changed by the time the present application was filed such that it was no longer unpredictable.

The Office Action further alleges that the specification, as filed, does not "provide sufficient guidance for one skilled in the art to make and/or use a representative number of bacterium from the genus Bifidobacterium as gene delivery vectors." The Office Action mentions that the specification provides "several working examples displaying the transformation of Bifidobacterium longum with a gene and the [delivery] of the genetically modified bacterium to tumor-bearing mice." In response, the Applicants note MPEP Section 2164.02, which states that "representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." Applicants reiterate that Argnani mentions that transformation in other Bifidobacterium species is possible using an *Escherichia coli-Bifidobacterium* shuttle vector. Taken together, one skilled in the art would recognize that the specification sufficiently provides representative examples, and the prior art, namely Argnani, indicates that the examples are applicable to the genus as a whole. As such, the Office Action

does not provide evidence that the instant invention would require undue experimentation due to the working examples and guidance provided by the specification.

The state of the art also indicates that the bacterium of the genus Bifidobacterium other than Bifidobacterium longum can be used. For example, Li et al. (Cancer Gene Ther 10: 105-111, 2003; submitted in IDS of September 28. 2006) relates to the use of Bifidobacterium adolescentis as a delivery system to transport antiangiogenesis genes to tumors. Thus, the instant invention would not require undue experimentation because of the state of the art.

Finally, to reiterate, Applicants note that Brown 1 presents an allowed claim relating to "nonpathogenic anaerobic microorganism" (claim 1) even though specification contains examples involving only one kind of bacteria (Clostridium acetobutylicum). Brown 1 is associated with the same technical category as the present invention, and the method mentioned in Brown 1 was developed at approximately the same time as the present invention. The present invention, similar to Brown 1, presents examples using one kind of bacteria (Bifidobacterium longum). In contrast, the claims of the present invention, unlike Brown 1, are focused to a bacterium of the genus Bifidobacterium, not to anaerobic microorganisms in general. Therefore, in view of Brown 1, a skilled artisan would recognize that the present claims are certainly enabled by the specification and would not require undue experimentation, especially if the state of the art indicates that the a presentation of one bacterium species is enabing of - at least- the genus.

Therefore, there is a failure to provide a factual showing that the present application is not enabled. Absent factual evidence corresponding to the *Wands* factors above, the Section 112 rejection is improper and must be withdrawn.

Accordingly, reconsideration and withdrawal of the 35 U.S.C. § 112 rejections are respectfully requested.

VI. REJECTIONS UNDER 35 U.S.C. § 103(a) ARE OVERCOME

Claims 28-46 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting 40: 88, 1999; hereinafter "Yazawa 2") in view of Brown et al. (U.S. Patent No. 6,416,754B1; hereinafter "Brown 2"). Applicants respectfully traverse this rejection.

According to the Office Action, Yazawa 2 refers to using Bifidobacterium longum as "a gene delivery vector for treating cancer in a buffer or solution" (considered to be a pharmaceutical preparation), but does not mention introducing DNA into a tumor in which the DNA codes for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance. The Office Action alleges that Brown 2 alludes to a "genetically modified bacterium to deliver an enzyme to the hypoxic/necrotic environment of a tumor and systematically administering a pro-drug, which is converted at the site of the tumor to the toxic agent by the enzyme."

In response, Applicants respectfully argue that given Brown 2 refers to the bacteria genus Clostridium and Yazawa 2 mentions Bifidobacterium longum, a skilled artisan would not combine Brown 2 with Yazawa 2 due to the considerable differences between Clostridium and Bifidobacterium. For instance Clostridium and Bifidobacterium.are members of different phyla (Firmicutes and Actinobacteria, respectively) and have notably different GC-content. : Functionally, these bacteria also induce different responses in the body. For example, Butel et al. (J Med Microbiol 47: 391-399, 1998) mentions that Clostridium may play a role in the pathogenesis of neonatal necrotizing enterocolitis while Bifidobacterium can exert a protection against the illness by inhibiting the growth of Clostridium strains. In fact, as indicated by Meer et al. (Rev Environ Contam Toxicol 150: 75-94, 1997) and Klingler et al. (Dig Dis 18: 147-160, 2000), Clostridium is often associated with digestive illnesses; even nonpathogenic bacterium of the genus Clostridium can experience back mutation to pathogenicity at a rate of 10^{-7}. In contrast, Bifidobacterium has been used to prevent antibiotic-associated diarrhea (see Elmer et al. JAMA 275: 870-876, 1996). Therefore, one skilled in the art would not combine the Yazawa 2 and Brown 2 references, as the state of the art at the time the application was filed indicates that Clostridium and Bifidobacterium are very different and are not interchangeable.

In addition, the present invention describes a gene delivery method that involves the vegetative form of Bifidobacterium. Recombinant DNA is introduced into Bifidobacterium, the bacteria are then cultured, and transformed bacteria are administered into tumors in the vegetative form (see, for example, Example 2). In contrast, Brown 2 describes a method of gene delivery involving sporulation, stating that "antitumor activity is optimally produced by spores rather than the vegetative form" and that "C. acetobutylicum produces spores under the conditions present in the targeted tumor" (paragraph 0147). This sporulation method is also

described in Examples 1, 2, and 4 of Brown 2. Further, there is a possibility that spores can randomly transfer to normal tissues. Brown 2's recitation that the spore form is the optimal embodiment teaches away from the vegetative form of bacteria used in the present invention. Therefore, Brown 2 teaches away from the present invention.

Finally, Applicants note that claim 28 recites in part (4) that the cloning vector "has a selective marker that can detect specifically a bacterium belonging to the genus Bifidobacterium being transformed with the cloning vector." Neither Yazawa 2 nor Brown 2 teach or suggest including a marker that can detect a bacterium belonging to a specific genus. In fact, the present invention discloses the secretion of cytosine deaminase in tumors, which is not mentioned in the references cited in the Office Action. Furthermore, Yazawa 2 and Brown 2 also do not teach or even suggest that (i) a cloning vector is involved in expressing a gene encoding a histone-like DNA binding protein of a bacterium of the genus bacterium, as disclosed in claim 31; (ii) the promoter and terminator are involved in expressing a gene encoding a histone-like DNA binding protein derived from Bifidobacterium longum, as disclosed in claim 32; (iii) a cloning vector having a promoter and terminator comprising nucleotides 1 to 192 of SEQ ID No: 1 and nucleotides 472 to 600 of SEQ ID No: 1 as disclosed in claim 33; (iv) the cloning vector is pBLES 100 as disclosed in claim 34; (v) a bacterium belonging to the genus Bifidobacterium as a gene delivery vector which is Bifidobacterium longum 105A/pBLES100-S-eCD, represented by the accession number FERM BP-7274, as disclosed in claim 40. As indicated in the MPEP, Section 2143.03, in order to establish prima facie obviousness of a claimed invention, "all the claim limitations must be taught or suggested by the prior art." Therefore, the combination of Yazawa 2 and Brown 2 is not obvious over the present invention.

Accordingly, reconsideration and withdrawal of the 35 U.S.C. § 103 rejections are respectfully requested.

REQUEST FOR INTERVIEW

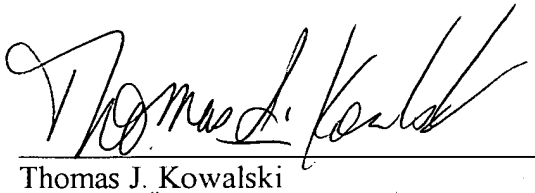
If any issue remains as an impediment to allowance, an interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: 

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